Epinephrine, Self-Injected Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
epinephrine 0.3 mg (EpiPen®)[1,2]	generic* Mylan Specialty	▪ Emergency treatment of Type I allergic reactions including anaphylaxis to stinging insects, biting insects, allergen immunotherapy, foods, drugs, diagnostic testing substances, and other allergens ▪ Emergency treatment of idiopathic anaphylaxis ▪ Emergency treatment of exercise-induced anaphylaxis
epinephrine 0.15 mg (EpiPen Jr.®)[3,4]	generic* Mylan Specialty	

*The generic epinephrine by Impax/Lineage is an authorized generic of Amedra's/Impax's Adrenaclick® manufactured in small quantities. Adrenaclick is no longer manufactured in sufficient quantities to meet demand, and Amedra/Impax is anticipated to cease manufacturing the product; supplies are expected to be depleted in the near future.[5] The generic epinephrine by Impax/Lineage is not interchangeable for EpiPen (BX rating).

Auvi-Q®, an epinephrine auto-injector approved in 2012 from Sanofi U.S., was recalled in October 2015 due to potentially inaccurate dosage delivery.[6,7] The development agreement between Sanofi U.S. and the developer of Auvi-Q, Kaléo, has terminated. Kaléo has not announced decisions or timing regarding market return.[8]

OVERVIEW

Anaphylaxis is an acute, life-threatening medical emergency with many potential triggers. According to the 2010 diagnosis and management of anaphylaxis practice parameter and the 2015 update, anaphylaxis is currently defined as 1 of 3 scenarios based on the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) criteria:

- The acute onset of a reaction (minutes to several hours) with involvement of the skin, mucosal tissue, and at least 1 of the following: a) respiratory compromise; or b) reduced blood pressure; or c) symptoms of end-organ dysfunction; or
- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient – involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure, symptoms of end-organ dysfunction, and/or persistent gastrointestinal symptoms; or
- Reduced blood pressure after exposure to a known allergen for minutes to several hours.[9,10]

Anaphylaxis may be fatal and requires prompt recognition and immediate management.[11] Anaphylaxis has a rapid onset with multiple organ-system involvement and is primarily seen in sensitized individuals after exposure to specific antigens. Reactions typically follow a uniphasic pattern; however, about 20% of reactions will be biphasic in nature. The second phase usually occurs after an asymptomatic period of 1 to 8 hours with as much as a 24-hour delay. According to the 2010 National Institute of Allergy and Infectious Diseases (NIAID)-Sponsored Food Allergy Guidelines, intramuscular epinephrine is the treatment of choice for all instances of anaphylaxis resulting from food or any other cause.[12] Patients with a history of an anaphylactic reaction and those at an increased risk of anaphylaxis should receive a prescription for an epinephrine autoinjector.[13,14] It should be administered immediately at first signs or symptoms of anaphylaxis. Although epinephrine has a rapid onset of action, it is also quickly metabolized. Therefore, repeat dosing may be necessary if anaphylactic symptoms do not fully resolve in 5 to 15 minutes. Patients should carry 2 doses of epinephrine. More than 2 sequential doses of epinephrine should only be administered under direct medical supervision. Protracted anaphylaxis may persist beyond 24 hours. Concurrent beta-blocker therapy may adversely affect the response to

management. Secondary measures include circulatory support, antihistamines (both H_1 and H_2 antagonists), corticosteroids, and, occasionally, bronchodilators. Careful post-treatment observation of patients who suffer an anaphylactic episode is necessary with ready access to emergency care for the following 48 hours. Patients who experience hypotension should remain recumbent until hemodynamically stable or asymptomatic, due to an increased risk of sudden death upon sitting upright prematurely.[15]

Anaphylaxis may occur as a result of exposure to specific agents (e.g., food, medication, or insect bites/stings).[16] Patients should be educated about specific exposures that may place them at risk for future reactions. They should also be provided counseling on avoidance measures to reduce risk for such exposures. Patients who have experienced anaphylaxis should carry self-injectable epinephrine for emergency use. These patients should also carry identification indicating they are prone to anaphylaxis and indicate the responsible agent.

PHARMACOLOGY[17]

Epinephrine acts on both alpha- and beta-adrenergic receptors. By acting on the alpha-adrenergic receptors, epinephrine reduces vasodilation and increases vascular permeability that occurs during anaphylaxis which alleviates loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation which alleviates bronchospasm, wheezing, and dyspnea that may occur during anaphylaxis. Epinephrine may also be useful in reducing urticaria, pruritus, angioedema, and gastrointestinal/genitourinary symptoms associated with anaphylaxis as a result of its relaxing effects on the smooth muscle of the stomach, intestines, uterus, and urinary bladder.

PHARMACOKINETICS[18]

Drug	Route of Administration	Onset of Action	Duration of Action
epinephrine (EpiPen, EpiPen Jr., generic)	SC	5 to 15 minutes	1 to 4 hours
	IM	Variable	1 to 4 hours

CONTRAINDICATIONS/WARNINGS[19,20]

There are no absolute contraindications for the use of epinephrine in life-threatening situations; however, patients with cardiovascular disease, hyperthyroidism, diabetes, elderly individuals, pregnant women, and patients with Parkinson's disease are more prone to adverse effects when using self-injectable epinephrine. In cardiovascular disease, epinephrine may precipitate or aggravate angina pectoris, in addition to causing ventricular arrhythmias. Thus, epinephrine should be administered with caution in such patients. Generic epinephrine, EpiPen, and EpiPen Jr. contain sulfites. The presence of a sulfite in these products should not deter administration of the drug for treatment of serious allergic or other emergency situations, even if the patient is sulfite-sensitive. Another precaution that should be addressed when using epinephrine self-injectable products is to avoid accidentally injecting into one's fingers, hands, or feet because this could cause vasoconstriction resulting in a loss of blood flow and hypothermia in the affected area and may require medical attention. Epinephrine should not be injected into the buttocks. Injection in this location may not provide effective treatment of anaphylaxis. Immediate emergency anaphylaxis treatment must be sought via the nearest emergency room.

Epinephrine must not be injected intravenously. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to a quick rise in blood pressure.

DRUG INTERACTIONS[21,22,23]

Epinephrine should be used cautiously in patients receiving any of the following drugs due to the increased risk of adverse effects, including cardiac arrhythmias: albuterol, dobutamine, dopamine, isoproterenol, metaproterenol, norepinephrine, phenylephrine, phenylpropanolamine, pseudoephedrine, ritodrine, salmeterol, and terbutaline. Certain types of antidepressants, such as tricyclic antidepressants and monoamine oxidase inhibitors, along with thyroid hormone replacement and certain antihistamines, particularly chlorpheniramine, tripelennamine, and diphenhydramine, may also potentiate epinephrine physiological effects. Likewise, beta-adrenergic blocking drugs, such as propranolol, may antagonize the cardio stimulating and bronchodilating effects of epinephrine. Alpha-adrenergic blocking drugs, such as phentolamine, may antagonize vasoconstricting and hypertensive effects of epinephrine. Ergot alkaloids may also reverse the vasoconstricting effects of epinephrine. Patients taking cardiac glycosides, diuretics, or anti-arrhythmics while receiving epinephrine should be observed carefully for the presence of cardiac arrhythmias.

ADVERSE EFFECTS[24,25,26]

Adverse reactions to epinephrine may include transient central nervous system (CNS) symptoms, such as anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, and/or headache. Other adverse effects may include sweating, palpitations, pallor, nausea/vomiting, and/or respiratory difficulties. These effects usually subside quickly, with rest and recumbent position. Although these reactions may occur in patients receiving therapeutic doses, they are more likely to occur in patients with hypertension or hyperthyroidism. Cardiovascular adverse effects, such as arrhythmias and rapid rises in blood pressure, have been observed in patients receiving epinephrine products. Arrhythmias, such as fatal ventricular fibrillation, have been reported and have been fatal in some instances in patients with underlying cardiac disease or utilizing certain drugs. Furthermore, rapid increases in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with underlying heart disease. Angina may develop and/or worsen in patients with coronary artery disease. Accidental injection into the fingers, hands, or feet may result in loss of blood flow to the affected area. There are a number of adverse events that may be experienced as a result of accidental injections, such as increased heart rate, local reactions, including injection site pallor, coldness, and hypoesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema, or skeletal injury. It should be noted that, in an acute life-threatening allergic reaction, the potential for epinephrine to produce the types of adverse reactions stated above, does not contraindicate its use.

SPECIAL POPULATIONS[27,28]

Geriatrics

Elderly patients are more prone to adverse effects when using epinephrine and should therefore use self-injectable epinephrine with caution. This is especially true for geriatric patients with underlying cardiovascular and/or metabolic disease.

Pediatrics

The self-injectable epinephrine products in this category are approved for use in children based on body weight. Please consult the individual package inserts for specific product information.

Pregnancy

Epinephrine is Pregnancy Category C.

Renal Impairment

There are no specific recommendations for dosage adjustments necessary for patients with impaired renal function. Please consult the individual package inserts for specific product information.

Hepatic Impairment

There are no specific recommendations for dosage adjustments necessary for patients with impaired hepatic function. Please consult the individual package inserts for specific product information.

DOSAGES[29,30]

Drug	Patient Weight of 30 kg or more (66 pounds or more)	Patient Weight of 15 to 30 kg (33 to 66 pounds)	Availability **Special Note:** Inject IM or SC in the anterolateral aspect of the thigh, through clothing if necessary. Time to Cmax is shortest when administered IM to the lateral aspect of the thigh.[31]
epinephrine (EpiPen, EpiPen Jr.)	0.3 mg injection	0.15 mg injection	**Generic:** 0.15 mg/0.15 mL, 0.3 mg/0.3 mL ▪ 0.15 mg/0.15 mL, 0.3 mg/0.3 mL; each strength packaged with 2 auto-injectors; training devices for the generic are available to order ▪ Individual devices are intended for a single administration, remaining volume should be discarded; more than 2 subsequent doses should be administered under direct medical supervision **EpiPen:** 0.3 mg (0.3 mL; 1:1000) **EpiPen Jr.:** 0.15 mg (0.3 mL; 1:2000) ▪ Dual packs of both EpiPen and EpiPen Jr. (EpiPen 2-Pak and EpiPen Jr. 2-Pak) are available with 2 auto-injectors and 1 auto-injector trainer device ▪ Individual devices are intended for a single administration, remaining volume should be discarded; more than 2 subsequent doses should be administered under direct medical supervision

Generic epinephrine, EpiPen, and EpiPen Jr., are only available as double packs. More than 2 sequential doses of epinephrine should only be administered under direct medical supervision.

DEVICES[32,33]

These products are intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care.

Epinephrine injection and auto-injectors each contain 1.1 mL of epinephrine solution, delivering either 0.15 mg (0.15 mL) or 0.3 mg (0.3 mL) of epinephrine in a single administration. The remaining volume should be discarded.

EpiPen and EpiPen Jr. auto-injectors each contain 2 mL of epinephrine solution. Approximately 1.7 mL remains unusable after activation. Each EpiPen delivers 0.3 mg epinephrine in a single dose. Each EpiPen Jr. delivers 0.15 mg epinephrine in a single dose.

EpiPen, EpiPen Jr, and epinephrine auto-injectors contain visual instructions on the devices.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no comparative trials currently available for the self-injectable epinephrine products.

SUMMARY

Anaphylaxis is a life-threatening allergic reaction that can be caused by a variety of allergens including food, medications, insect stings and bites, and latex. All patients at risk of anaphylaxis are urged to carry self-injectable epinephrine (EpiPen, EpiPen Jr., or generic). Patients should be well informed by their physician and/or pharmacist of when to use this life saving medication.

Each of the self-injectable epinephrine devices allows patients to deliver a single dose from the unit via auto-injection. The generic formulation currently available is not interchangeable for EpiPen.

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